Chapter

The Gout

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Abstract

Gout is a form of arthritis in an individual accompanied with symptoms like severe pain, stiffness, and swelling of one or more joints. Factors that influence rates of gout are many like drinking alcohol, being overweight, drinking soda, becoming dehydrated, the weather, poorly fitting shoes, medical treatments, and many more. The root cause of this condition mainly we can say is the disorder of purine metabolism. There are diagnostic options like synovial fluid test, blood test for uric acid, and differential diagnosis. Preventive measures can include both lifestyle changes and medications. In a recent trend, many treatment options are available like the use of NSAIDs, colchicine, steroids, etc. Common drugs which are on use are probenecid, allopurinol, febuxostat, and pegloticase. Our medical fraternity and researchers are continuing to work on further development.

Keywords: gout, arthritis, purine, uric acid, metabolism

1. Introduction

Gout is a disease condition which often is considered as a form of inflammatory arthritis [1–4]. Unlike arthritis, gout is not a degenerative process. It's generally characterized by frequent attacks of swelling [5, 6], redness, and a tender, warm, and puffy expression of bone joint areas. **Figures 1–3** represent a few gouty expressions. The joints of limbs especially lower limbs, at the base part of the big toe and at the first joint of forefingers of upper limbs, are affected. Some other complications associated are like tophus, urate nephropathy, or kidney stones.

Gout is the result of persistently increased levels of uric acid in the blood [7]. An enzyme named xanthine oxidase is mainly responsible for the production of uric acid in our body. **Figure 4** explains the synthesis pathway of uric acid. As the uric acid concentration becomes high, it undergoes crystallization, and the crystals get deposited in joints. Thus, the surrounding tissues get affected which may lead to redness, swelling, and inflammation, resulting in an attack of gout.

2. Cause

Gout is a result of a disorder in purine metabolism. When there is an increase in the uric acid level in blood, there is a chance of crystallization of uric acid. Such crystals are deposited in joints which start showing the symptoms of gout. The predominant reason of increased level of blood urea is the reduced amount of excretion of uric acid from the body. Synthesis of excessive amount of uric acid may be another reason for increased level in blood, but the cases are more where the first reason is predominant. The risk of developing the symptoms is more

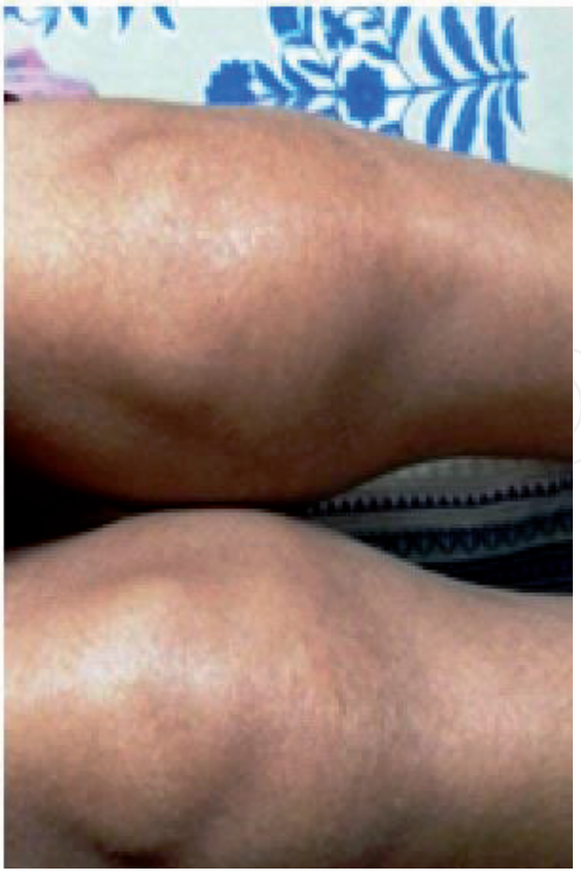

Figure 1.
Swelling in the knee.

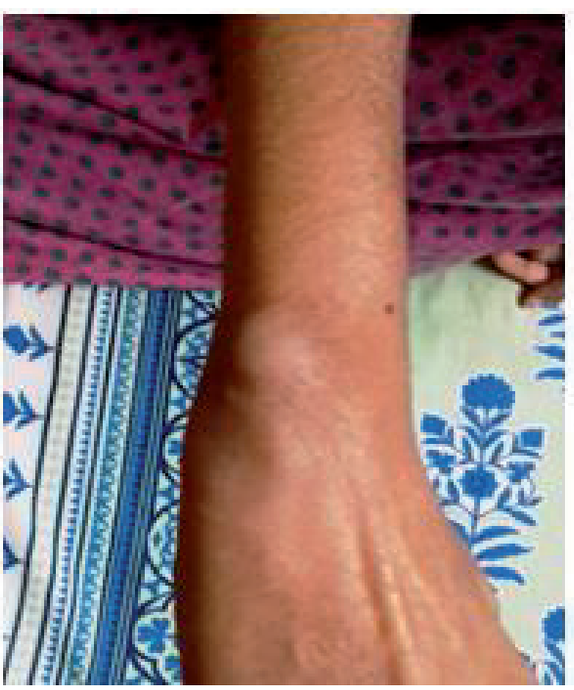

Figure 2.
Puffy wrist (ulna).

and faster as the concentration of uric acid increases. The normal uric acid level in the human body is 2.4–6.0 mg/dL in the case of female and 3.4–7.0 mg/dL in the case of male. When levels are between approximately 7 and 8.9 mg/dL, the

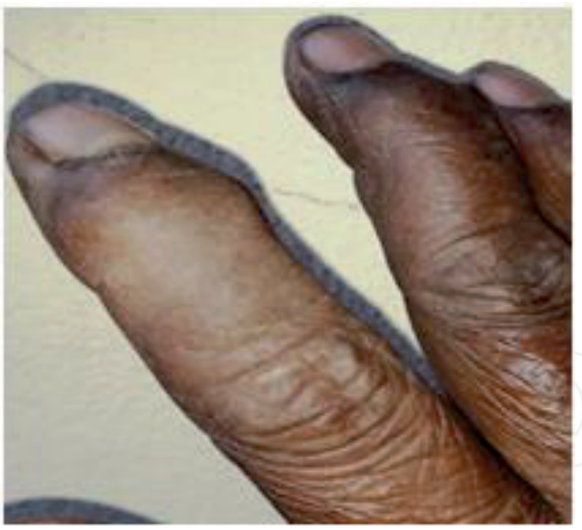

Figure 3.
Swelling and stiff finger.

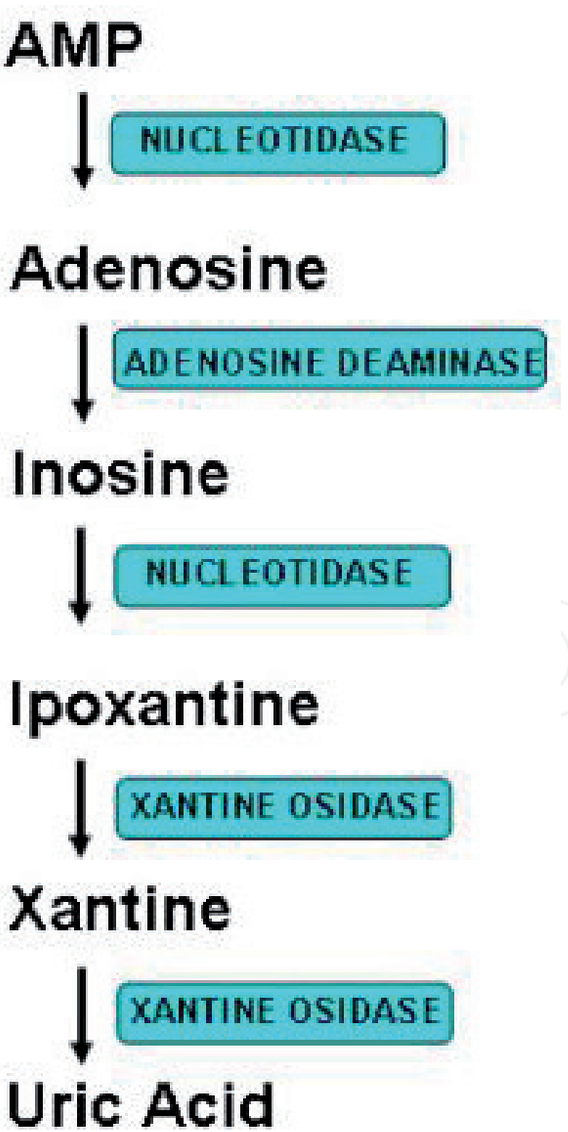

Figure 4.
Part of uric acid pathway.

approximate risk is 0.5% per year. The risk may extend up to 4.5% in those with a level more than 9 mg/dL [8].

Uric acid, when it is in higher level in blood, crystallizes in the form of a salt, monosodium urate, precipitating and making deposition in joints, on tendons, and also in the surrounding tissues. These deposits may be walled off by the ring of certain proteins, which can block the interaction of these crystals with cells and therefore can avoid inflammation. Crystals may break and be displaced out due to the minor physical stress-related damage to the joint like medical or surgical stress or otherwise rapid changes in uric acid levels or so. When they disintegrate through the tophi, they stimulate a local immune-mediated physical-chemical inflammatory reaction in macrophages. This is initiated by an inflammation-mediating protein complex named NLRP3. In the mechanism of inflammation, a protein named interleukin 1β plays an important role which is obtained from pro-interleukin 1β with the help of enzyme caspase 1. NLRP3 assists the enzyme in its function.

3. Diagnosis

Sign and symptoms of arthritis may motivate the physician to go for examination of the patient. It can be diagnosed by different investigational methods. Patients with hyperuricemia can receive treatment based on the diagnosis and their severity. Different types of diagnosis are mentioned as follows.

3.1 Blood tests

Since hyperuricemia is a cause for uric acid crystallization and deposition of the same on joints, examination of blood sample is a common and initial process observed in orthopedic clinics [9, 10]. But sometimes it's observed that gout occurs without hyperuricemia also and many people with increased uric acid levels did not develop gout. Thus, the usefulness of the diagnosis of measuring uric acid levels in many individuals is limited. The normal uric acid level in blood is ranging around or less than 420 μmol/L (7.0 mg/dL) in males and 360 μmol/L (6.0 mg/dL) in females. Therefore, above this margin of uric acid in blood may be considered as hyperuricemia. Other blood sample investigations commonly performed are erythrocyte sedimentation rate (ESR), white blood cell count, kidney function and electrolyte tests.

3.2 Synovial fluid

A qualitative investigation of gout is based upon polarimetric analysis of crystals of monosodium urate [11]. These crystals are deposited on the joints of a hyperuricemic patient. A synovial fluid sample is collected from undiagnosed inflamed joints with the help of arthrocentesis. The fluid is sampled appropriately to examine these crystals. In a polarimeter the sample is studied to check the needle-like morphology as well as strong negative birefringence.

3.3 Miscellaneous methods

There are certain investigations which may or may not be directly related to arthritis but definitely prove beneficial most of the time [12]. Detection for psoriatic arthritis is one of them. Since it can affect joints on either one side or both sides of our body, the signs and symptoms of this often resemble those of arthritis. The disease causes joints to become painful, swollen, puffy, and warm

to the touch. Another important test is for septic arthritis. This may be accompanied by joint infection. Naturally the disease results in joint inflammation. Other symptoms typically include heat, redness, and pain in a single joint which may be associated with a decreased ability in moving the joint. One more diagnosis may be recommended, and that is to test for reactive arthritis. This can affect the heels, fingers, toes, low back portion, and joints, especially of the ankles and knees [13, 14].

4. Preventive measures

In mild to moderate cases of gout, lifestyle changes can decrease uric acid levels in blood. These modifications may include selection of correct diet, regular and appropriate exercise, and consultation with a physician. Physiotherapy also can help in this regard.

4.1 Food habit

Appropriate diet is very important [15]. Overweight is a big factor causing joint pain [16]. Food containing high amounts of purine such as seafood like shellfish, anchovies, sardines, herring, codfish, mussels, scallops, trout haddock, etc.; some meats, such as turkey, bacon, veal, venison, and organ meats like liver, etc. [17]; and drinks and beverages like beer or all types of alcoholic beverages, containing high amounts of purine, can increase blood urea level [18]. Soft drink contains either fructose or sucrose in huge quantity which may enhance the precipitation of uric acid crystals. Therefore, reducing or omitting such products from the diet list is advisable.

4.2 Sleep apnea

As there is a chance of deficiency of oxygen in the cell due to improper breathing or irregular breathing style during sleep, it may stimulate the release of purine from those cells, and therefore a control on sleep apnea may help in the control of gout.

4.3 Dehydration

Becoming dehydrated may also be a reason of gout risk. Exact mechanism is not clear, but it is believed that it may increase the concentration of uric acid in reduced volume of blood and also in the joint fluid. Hence, consuming adequate amount of water is advisable.

4.4 Obesity

Obesity, diabetes, and increased cholesterol are conditions quite commonly seen together. If these two disorders become contemporary in a patient, he or she may land up with a metabolic syndrome. Such patients frequently also have an elevated level of uric acid in their blood. In certain time diuretics prescribed to control high blood pressure also can cause higher levels of uric acid.

4.5 Drinking soda

Carbonated water for drinks or drinking soda has a high-fructose corn syrup which is a culprit in elevating uric acid levels, thereby increasing gout risk.

4.6 Kidney stones

In a certain time, kidney stone may get traces of uric acid. In such cases if dehydration takes place in the patient's body, then precipitation of uric acid becomes more severe. To prevent dehydration, drinking sufficient amount of water a day is very essential.

4.7 Poorly fitting shoes

Wearing the wrong shoes can become another gout-triggering factor. Any kind of trauma or damage to an area can cause a gout pain and swelling in susceptible people. If our shoes rub the toe or nearby area of our feet, then it can contribute to a gout attack. So it is better to make sure that the toe area of our shoes is wide enough so that it can accommodate our feet without pinching or rubbing.

4.8 Medical treatments

Toxic effect of some drug substances can contribute in hyperuricemia. These drug substances are recommended for patients for certain disease conditions where they are certainly beneficial but may result in elevated uric acid level. Diuretics can decrease the removal of uric acid from our body and cause hyperuricemia, thereby a risk factor to develop gout. In the treatment of carcinoma, chemotherapy may lead to the breakdown and rapid turnover of tissue cells and can lead to increased synthesis of uric acid. In case of surgery, a sudden severe physiological change that causes reduced blood flowing to the area of peripheral joints can also be a risk factor for gout. Therefore, adequate amounts of precautions are required while receiving treatment.

5. Medications

Many drug substances are available for the treatment of hyperuricemia. As a first-line therapy along with these drugs, a compound is to be recommended which can cause a symptomatic relief. One of the best choices is an anti-inflammatory agent.

Available drugs recommended for reducing hyperuricemia are allopurinol, febuxostat, probenecid, pegloticase, lesinurad, etc.

Allopurinol is a structural isomer of hypoxanthine (a naturally existing purine in our body) and acts to inhibit an enzyme xanthine oxidase [19]. In the presence of this enzyme, allopurinol will be converted to a compound named alloxanthine, and thereby the formation of uric acid from hypoxanthine and xanthine will be inhibited.

Febuxostat is not a purine-based compound but a selective inhibitor of enzyme xanthine oxidase [20–24]. In contrast to allopurinol, this compound inhibits both oxidized and reduced forms of enzyme xanthine oxidase and has minimal effects on other enzymes of pyrimidine and purine metabolism. A study comparing febuxostat to allopurinol revealed that more individuals receiving febuxostat had a decreased uric acid level.

Therapeutically, probenecid is generally coadministered with other pharmacologically active substances such as anti-inflammatory drugs or penicillins resulting in a substantial diminished renal clearance of all these compounds [25–28]. In higher doses than are actually required for the uricosuric effect, probenecid can inhibit the transport system which removes acid substances from the cerebrospinal

fluid. Probenecid also increases the urinary excretion of uric acid and therefore has a therapeutic value for the ailment of gout.

Pegloticase is a third-line treatment option for those in whom other treatment options are not tolerated [29]. Generally it is an option for the treatment of chronic, severe, treatment-refractory gout. Pegloticase, a PEGylated, recombinant uricase enzyme, converts salt of uric acid into allantoin. Thus, it makes a wonderful job by increasing the excretion of uric acid through kidney filtration.

Lesinurad is a drug of choice to be recommended together with either febuxostat or allopurinol when these medications are not sufficient as monotherapy [30, 31]. It reduces urate transport by inhibiting a protein named URAT1 that is responsible for much reabsorption of uric acid or urat in the kidneys. It also inhibits the OAT4 protein, which is associated with hyperuricemic condition caused by diuretic drugs.

A confirmation about a gout case is given by medical experts only after certain tests are conducted and analyzed. Prior to the investigation, a physician can go for a symptomatic relief for the suffering patients by providing a simple prescription containing simple anti-inflammatory or analgesic drugs (NSAIDs) [32, 33]. Common compounds are like acetaminophen, ibuprofen, indomethacin, ketorolac, piroxicam, mefenamic acid, etc. A selective COX-2 inhibitor can be a better choice in case a physician looks for the therapy for beyond 1 week. These drugs include meloxicam, celecoxib, rofecoxib, etoricoxib, etc. All the abovementioned drugs come under nonsteroidal anti-inflammatory drugs. With similar efficacy corticosteroidal drugs also are also recommended as a co-prescription for symptomatic control. Both glucocorticoids and mineralocorticoids can be prescribed depending on the case demand. Some examples of synthetic corticosteroids are betamethasone, prednisone, prednisolone, triamcinolone, methylprednisolone, dexamethasone, and systemic (oral and injectable) steroids that are available for use including hydrocortisone, cortisone ethamethasoneb, fludrocortisone, etc. For those patients unable to tolerate NSAIDs, colchicine is an ideal alternative. Colchicine is a category of substance which is effective at lower dose, and it is well tolerated [34]. It may interact with some other commonly prescribed drug substances, such as erythromycin and atorvastatin, simvastatin, etc.

6. Conclusion

Gout is a form of disease which may be acute or chronic, associated with symptoms like severe pain, stiffness, and swelling of one or more joints. It occurs due to increased production of uric acid in our body or reduced excretion of the same from our body. Such metabolic disorder may arise from poor lifestyle and improper food habits. A number of diagnostic options are available and treatment too. But it's always advisable to adapt a healthy food habit, practice physical exercise, and continue with physician's consultation and medication to get rid of this disease condition.

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